will result in increased lactic acid production.[215,219,220]

Patients with diabetes mellitus have an increased disposition toward increased lactic acid levels. This is often due in these patients to significantly increased cardiovascular disease with associated tissue hypoxia or may be due to increased lactic acid production associated with phenformin administration.[214,215,221] Lactic acidosis in the diabetic is often associated with poor control as evidenced by hyperglycemia but may be associated at times with normoglycemia,[216] or even hypoglycemia.[217,218]

Since phenformin is a commonly used drug in the treatment of diabetes, further comment on its potential role in the pathogenesis of lactic acidosis is appropriate. There is little question that phenformin administration results in increased production of lactic acid both in diabetic and in nondiabetic persons.[221-223] This effect appears to be due to inhibition of cellular aerobic metabolism[224] and is dose-related.[214] While increases in levels of serum lactic acid occur commonly in the upper part of the therapeutic dosage range, the production of clinically important lactic acidosis is unusual in the absence of other precipitating events. The majority of the patients described with phenformin-associated lactic acidosis had a history of alcohol excess, were in shock or had other reasons for tissue hypoxia. There are reports of lactic acidosis attributable to phenformin taken in attempts at suicide.[191,221]

Whether or not phenformin in normal dosage may result in clinically significant lactic acidosis in the absence of other causal events, it is likely that it will aggravate lactic acidosis occurring from any other cause. This may be the result of additive effects of phenformin on lactic acid production or, more importantly, its effect on decreased removal of circulating lactic acid.[222] For these reasons, phenformin therapy should be avoided in any patient with evidence of vascular disease.

Treatment of lactic acidosis has in general been disappointing. Emphasis must be placed on (1) early recognition; (2) elimination of the sources of lactate overproduction, such as correction of shock, hypoxemia, tissue hypoxia, anemia and elimination of precipitating drugs; (3) correction of acidosis with bicarbonate therapy, and (4) conversion of lactic acid to pyruvate by the administration of methylene blue.[225]

Diabetes, Pregnancy and Obesity

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IMPORTANT ALTERATIONS in maternal metabolism occur during pregnancy, and it is now generally agreed that these changes are largely mediated by placental hormones. These events have been looked upon, teleologically, as evolutionary changes designed to help guarantee a continuing transplacental supply of energy and growth substrate to the fetus. However, for the mother the net effect of these alterations tends to be catabolic or anti-insulin, with the result that pregnancy is a stress to a diabetic or pre-diabetic person. More specifically, fasting insulin levels and the plasma insulin response to glucose and tolbutamide increase progressively throughout gestation.[226-229]

Since the rate of insulin degradation is enhanced during pregnancy,[230,231] these increased basal and stimulated concentrations of insulin reflect increased insulin secretion. In addition, the tolerance to exogenous insulin is increased[232,233] and fasting plasma levels of FFA are elevated.[234] These changes indicate progressive insulin resistance and, in an insulin-dependent diabetic woman, insulin requirements near term are on the average increased by 60 to 75 percent.[234] This pancreatic stress is sufficient in many genetically predisposed persons to provoke gestational diabetes mellitus. The incidence of gestational and insulin dependent mellitus in pregnancy probably ranges between 1 and 2 percent.[235]

The mechanism of insulin resistance in pregnant women is not entirely clear. It is not attributable to decreased glycogen stores,[236] altered catecholamine metabolism,[237] increased cortisol secretion,[238] or increased secretion of pituitary growth hormone.[239-241] Rather, it appears to be secondary to placental secretion of chorionic somatomammotropin (HCS),[229,239,242] estrogens and progestins.[229,243-245]

HCS has both growth hormone and prolactin-

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like effects and has been shown to impair glucose tolerance in hypophysectomized rats, to inhibit peripheral glucose utilization in normal subjects despite increases in plasma insulin concentrations, and to stimulate FFA release from fat depots.[246,247] There also is evidence that HCS may directly stimulate the function of the pancreatic beta cells.[242,248] The increase in secretion of insulin observed in hypophysectomized rats after administration of HCS, however, does not appear to be mediated through changes in blood sugar.[242] Finally, the progressive increase in maternal levels of HCS during gestation coincides temporally with the increasing concentrations of plasma insulin and progressive augmentation of the insulin response to glucose.[228] Estrogens and progestins also produce insulin resistance[229,243-245] and will precipitate diabetes mellitus in genetically predisposed persons.[244,245] Maternal blood levels of these steroid hormones increase progressively during gestation in a manner generally parallel to the progressive hyperinsulinemia.

The incidence of maternal complications of pregnancy is increased significantly by diabetes mellitus; major among these are toxemia, hydramnios, and acidosis. However, infection, particularly of the urinary tract, proliferative retinopathy, and hypoglycemia, especially early in gestation, also are common. The incidence of major complications has been reviewed recently by Spellacy,[235] who collated data from 29 series of patients reported between 1953 and 1967 (Table 11). Mortality varied from zero to 4.8 percent, toxemia from 3 to 53.7 percent, hydramnios from 3.5 to 51.4 percent and acidosis from zero to 37.2 percent. Fetal mortality also was collated and is summarized in Table 12.[245] Abortions varied from 1.2 to 18 percent, fetal deaths from 1.6 to 38.1 percent, neonatal deaths from 3.3 to 15.5 percent. Total perinatal deaths varied in frequency from 7.9 to 44.8 percent,[245] and the mean value 19.8 percent (Table 12) is several times higher than the accepted control figure of about 3 percent. In addition, the incidence of congenital anomalies is increased from the average rate of about 2 percent to a mean value of 5.8 percent.[245]

In a general way the incidence of fetal anomalies and the increased fetal mortality can be correlated with the severity and duration of maternal diabetes mellitus.[249,250] Thus, Nelson, Gillespie and White[251] have proposed a classification (A through F, plus R) based on maternal age at onset, duration of disease, and presence of demonstrable vascular complications from which fetal risk can be estimated. This risk relates, basically, to the development and extent of placental disease. The pathologic changes observed in the diabetic placenta include subsyncytial edema, syncytial hyperplasia, avascularity of villi, and the deposition of periodic acid shift-positive material in vascular intima.[252,253] There is a high degree of correlation between the extent of these changes, assessed from placental biopsy, and perinatal morbimortality.[252] Thus, as functioning placental tissue is progressively reduced in volume, fetal survival is progressively compromised. For this reason, it is now recommended that diabetic patients have serial tests of placental function; the most commonly employed are measurements of maternal excretion of estriol and maternal blood levels of human chorionic somatomammotropin (HCS).[235,254] Falling levels of these placental hormones near term suggest placental insufficiency and indicate a need for terminating the pregnancy.

In addition to the increased incidence of fetal anomalies and the high perinatal mortality associated with the diabetic pregnancy, the newborn infant of the insulin dependent (IDM) or gestational diabetic mother (IGDM) has a high incidence of neonatal morbidity. Such infants appear obese and plethoric; they are large for gestational age; they manifest visceromegaly involving the heart, liver and spleen; and they have increased stores of body fat.[249,255-257] Most of these changes can be attributed to fetal hyperinsulinemia. The IDM or IGDM is born with pancreatic islet cell hyperplasia and manifests fasting hyperinsulinemia and augmented insulin responses to glucose, amino acid and tolbutamide.[258-261] Thus, one of the major neonatal complications is hypoglycemia[248,249,259,260] but other complications, including hyperbilirubinemia, hyaline membrane disease, and hypocalcemia, are more commonly observed than in the normal newborn.

It is assumed that chronic fetal hyperglycemia associated with chronic maternal hyperglycemia is responsible for the fetal islet cell hyperplasia and hyperfunction. Insulin is an anabolic hormone, and chronic hypersecretion *in utero* (where hypoglycemia is prevented by maternal to fetal transport of glucose) results in increased fetal growth and increased fetal lipogenesis. However, the relatively high incidence of hyperbilirubinemia and respiratory distress in IDM or IGDM cannot be attributed to hyperinsulinism. These complications are more likely related to prematurity since most

IDM or IGDM are delivered early either spontaneously or electively.

It is now quite clear that the fetal morbimortality associated with pregnancy in diabetics can be reduced by careful management. It is particularly important to avoid acidosis, since this complication is associated with a high rate (about 30 percent) of fetal death *in utero*.[235] The lowest perinatal mortality occurs in patients in whom the blood glucose is kept closest to normal.[235] Since there is no increase in fetal hazard with maternal hypoglycemia, it is possible to control the diabetic or gestational diabetic subject fairly strictly. Moreover, one expects insulin requirements to increase progressively, especially near term. A decrease in insulin requirements in a diabetic woman in the later weeks of pregnancy is a grave prognostic sign for the fetus,[262] probably reflecting decreasing placental function. Oral hypoglycemic agents are not recommended for use during pregnancy.[235]

In the genetically predisposed subject who develops gestational diabetes mellitus, glucose tolerance characteristically improves after parturition and normal glucose tolerance is evident within three to five weeks postpartum. However, in about 30 percent of such women diabetes mellitus will develop within five years and 60 percent will be diabetic within 12 years.[263,264] Moreover, White has shown that 7 percent of the infants of diabetic mothers have diabetes mellitus by age 20 years.[263] Thus, although diabetes mellitus in pregnancy carries only a small risk of maternal mortality, it is a serious risk to the fetus and the newborn, a major challenge to the physician and carries important prognostic implications.

Although the offspring of diabetic mothers are frequently obese, the offspring of non-diabetic obese mothers are usually not overweight. In a study of 99 obese children, Wolff[265] found that their birth weights were identical in frequency distribution to that of other children born in the same hospital. Bruch, in a study of childhood obesity, also noted that the birth weight of obese children was normal. In the large group of children studied by Mossberg,[266] there was a larger variance among the birth weight of obese children than among the normal group. Thus, most of the obese children fell in the normal group, but there appeared to be a group of obese children with birth weights which tended to be higher than would be expected from the variance of the normal birth weights.

The Role of Carbohydrate and Oral Agents in the Treatment of Diabetes Mellitus

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DIABETES MELLITUS may be treated by one or more of several means; these commonly include dietary manipulation, insulin, sulfonylureas and biguanides. While it is beyond the intent of this discussion to review the usual aspects of standard treatment of diabetes mellitus, we would like to comment on some recent information that modifies our usual approach.

Dietary therapy optimally consists of adjustment of body weight to ideal and a distribution of calories into three or four approximately equal portions. Before the advent of insulin, dietary therapy was the only means of treating diabetic patients; typically low carbohydrate, low caloric diets were utilized. Because of this experience in the pre-insulin era, relative carbohydrate restriction has been advocated since the advent of insulin. Certain recent observations in diabetics cast doubt on the usefulness of such restriction. In normal men, Himsworth[267] showed in 1935 that if the carbohydrate content of the diet were reduced, but calories maintained, carbohydrate tolerance was lessened. Conversely, increasing dietary carbohydrate raised carbohydrate tolerance.

Such observations, now more than 37 years old, have been amply verified in more recent studies published in 1967 and 1968 by Wales et al[268] and Ford et al.[269] Brunzell and his coworkers[270] in 1971 extended these studies to diabetic subjects. In a carefully controlled study, non-diabetic and diabetic persons ranging from 91 percent to 163 percent of ideal body weight were studied. All subjects ingested diets of 40 percent fat, 45 percent carbohydrate and 15 percent protein during control periods and no fat, 85 percent carbohydrate and 15 percent protein in the experimental periods. Surprisingly, fasting insulin concentrations, fasting glucose concentrations, glucose tolerance and integrated insulin secretion during glu-

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